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Registration Decision RD2013-24

Ipconazole

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Registration Decision for Ipconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Ipconazole Technical Fungicide, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide, containing the technical grade active ingredient ipconazole, to protect against seedling and soil-borne diseases on small grain cereals and corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

The detailed review for these products can be found in Evaluation Report ERC2011-04, *Ipconazole*. The conversion from conditional registration to full registration for these products were proposed in the consultation document[1] Proposed Registration Decision PRD2012-05, *Ipconazole*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for Ipconazole and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2012-05.

For more details on the information presented in this Registration Decision, please refer to the Proposed Registration Decision PRD2012-05, *Ipconazole* that contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act* "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Ipconazole?

Ipconazole is a triazole fungicide used to control various fungal species. This active ingredient is used as a seed treatment on small grain cereals and corn to control smuts, bunts, leaf stripe and seed and seedling diseases caused by *Fusarium* spp., *Cochliobolus sativus*, *Rhizoctonia solani*, *Rhizopus* spp., *Cladosporium* spp., *Aspergillus* spp., and *Penicillium* spp. Ipconazole is classified as a Group 3 fungicide that inhibits sterol biosynthesis in fungi.

Health Considerations

Can Approved Uses of Ipconazole Affect Human Health?

Products containing ipconazole are unlikely to affect your health when used according to label directions.

Potential exposure to ipconazole may occur through the diet (food and water), when handling and applying the product, or when entering treated sites. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

A detailed assessment of the toxicology database for ipconazole and its associated end-use products, Rancona 3.8 FS Fungicide, Vortex FL Seed Treatment Fungicide and Rancona Apex Fungicide, can be found in ERC2011-04. In response to issues identified in the conditional registration, the applicant submitted waiver requests to address concerns regarding the cancer assessment, as well as the absence of hormone measurements in the toxicology database. Waiver requests for a short-term immunotoxicity study in rodents and an acute neurotoxicity study in rats were also submitted to address the effects noted on the immune system and potential neurotoxic clinical signs observed at high doses of ipconazole.

A review of the information submitted in the waiver request on the cancer assessment and the effects in endocrine organs was conducted. The information was considered sufficient to address the concerns and no further data are required at this time. The endpoints selected for dietary and occupational risk assessments were revisited to address these conclusions.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and children 3-5 years old, the subpopulation which would ingest the most ipconazole relative to body weight, are expected to be exposed to less than 1% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from ipconazole is not of concern for all population subgroups.

An acute reference dose was determined for the population subgroup of females 13-49 years of age. An aggregate (food and water) dietary intake estimate for females 13-49 years old used less than 1% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

The storage stability data submitted to support the conversion from conditional to full registration are adequate. For the MRLs for this active ingredient, please refer to the Science Evaluation of ERC2011-04.

Occupational Risks From Handling Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide

Occupational risks are not of concern when Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide are used according to the label directions, which include protective measures.

Workers mixing and loading Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide, or treating seed, as well as workers handling and planting freshly treated seed, can come into direct skin contact with the active ingredient, ipconazole, in these products. Therefore, the labels specify that anyone handling Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide, contaminated equipment, or corn seed treated with these products, must wear long pants, a long-sleeved shirt and chemical-resistant gloves. The labels also require that closed mixing/loading equipment be used. For Rancona Apex Fungicide, workers handling the product, contaminated equipment or cereal seed treated with this product must wear long-sleeved coveralls over normal work clothing and chemical-resistant gloves and, for commercial operations, closed mixing/loading equipment is required. Taking into

consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Ipconazole is Introduced Into the Environment?

Environmental risks are negligible when Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide are used according to label directions, which include precautionary label statements concerning soil incorporation of treated seed and cleanup of spilled seed.

Ipconazole can enter the environment by dislodging from treated seed surfaces during and after seeding. Ipconazole is persistent in the environment, with soil biodegradation being the primary route of transformation. Ipconazole has low mobility in soil, and has low potential to leach to groundwater. Ipconazole is not expected to reach surface waters in any appreciable amounts under the current use pattern, as exposure of surface waters through soil runoff and leaching is expected to be minimal. Some toxicity occurred to laboratory animals exposed to ipconazole; however, the primary environmental risk under the current use pattern is to birds and mammals that may consume treated seed. This risk was determined to be negligible if label statements regarding soil incorporation of treated seed and cleanup of spilled seed are followed. Risk to other terrestrial and aquatic organisms, and non-target plants is negligible based on low potential for exposure to these organisms.

Value Considerations

What Is the Value of Rancona Apex Fungicide, Rancona 3.8 FS Fungicide, and Vortex FL Seed Treatment Fungicide?

Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are seed treatments for use on field corn, sweet corn and popcorn to provide protection against seed, seedling and soil-borne diseases. Rancona Apex Fungicide is a seed treatment used to control diseases on cereals including wheat, barley, oats, rye and triticale.

Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are alternatives to several older chemicals currently used as corn fungicide seed treatments. As seed treatments, the rate per hectare of all of these products is low and application to the seed reduces exposure to non-target organisms compared to foliar pesticide applications. Rancona Apex Fungicide is a liquid seed treatment with a low concentration of active ingredient and is effective at low rates. Seed and seedling diseases on cereals can be adequately controlled using Rancona Apex Fungicide.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the labels of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with ipconazole on the skin or through inhalation of dusts, anyone handling Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide, contaminated equipment, or corn seed treated with these products, must wear long pants, a long-sleeved shirt and chemical-resistant gloves. The labels also require that closed mixing/loading equipment be used. For Rancona Apex Fungicide, workers handling the product, contaminated equipment or cereal seed treated with this product, must wear long-sleeved coveralls over normal work clothing and chemical-resistant gloves. Closed mixing/loading equipment is required for the commercial use of Rancona Apex Fungicide.

Environment

The use of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide may pose a risk to birds and mammals that consume sufficient amounts of treated seed. Precautionary label statements on the product labels identify and mitigate this risk (i.e. soil incorporation of treated seed and cleanup of spilled treated seed).

Other Information

The relevant test data on which the decision is based (as referenced in the Proposed Registration Decision PRD2012-05, *Ipconazole* and the Evaluation Report ERC2011-04, *Ipconazole)* are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticide and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision, www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/publi-regist/index-eng.php#rrd) or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

The registrant submitted comments on the conclusions and/or data in the documents, Proposed Registration Decsion, PRD2012-05, *Ipconazole*, and on the Evaluation Report, ERC2011-04, *Ipconazole*.

Comment on 3.4.1 Toxicological Endpoints

Short-term and Intermediate-term Dermal

The registrant provided a rationale for the use of the NOAEL from the rat dermal toxicity study to estimate dermal risk for all scenarios based on the United States Environmental Protection Agency (USEPA) assessment. The registrant requested that the PMRA consider the 28-day dermal toxicity study in rats with NOAEL of 150 mg/kg bw/day and the LOAEL of 1000 mg/kg bw/day with an uncertainty factor of 100× in the assessment.

PMRA Response

The PMRA reviewed the 28-day dermal toxicity study in rats (PMRA document number1368595) and concluded that the NOAEL is 150 mg/kg bw/day and the LOAEL is 1000 mg/kg bw/day. The PMRA does not consider it appropriate to estimate dermal absorption by comparing LOAELs in toxicity studies as the sole source on which to base this estimate. Since a NOAEL from an oral study was selected, a dermal absorption factor of 100% (default value) was used for route to route extrapolation. In addition, the effects of concern, decreased fetal weights and increased developmental malformations, were not assessed in the 28-day dermal toxicity study in rats and therefore, the oral rabbit developmental toxicity study was recommended for the short-term and intermediate-term dermal risk assessment.

As outlined in PRD2012-05, an additional factor of 3-fold for the concerns regarding seriousness of the endpoint in the presence of maternal toxicity, was applied when using the rabbit developmental toxicity study as the point of departure for assessing risk to women of child-bearing age and their fetuses. This approach is consistent with PMRA's Science Policy Note SPN2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*.

Short-term and Intermediate-Term Inhalation

The registrant provided a rationale for an alternate approach to assess the short-term inhalation based on the assessment conducted by the USEPA. An absorption factor of 42% was calculated by the USEPA based on a comparison of the LOAEL from the 90-day oral toxicity study in rats (PMRA Document Number 1368584) and the 28-day rat inhalation toxicity study LOAEL (78.3 mg/kg/day) (PMRA document number 1368601). This absorption factor was applied to the oral NOAEL from the developmental study in rats (10 mg/kg/day) to estimate the oral equivalent dose (24 mg/kg/day). Based on the similarities between the oral equivalent dose and the NOAEL from the inhalation toxicity study, it was concluded that the use of the inhalation NOAEL will be protective of potential effects to fetuses. The registrant requested that the PMRA consider these results for calculation of absorption factor, the NOAEL from 28-day inhalation study and the uncertainty factor of 100×.

PMRA Response

The PMRA reviewed the 28-day inhalation toxicity study in rats (PMRA document numbers 1368600 and 1368601) and concluded that the LOAEL is 8 mg/kg bw/day, the lowest dose tested. A NOAEL was not established. Since an oral endpoint was selected for the short-term and intermediate-term inhalation risk assessment, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation. It is not the PMRA's practice to estimate inhalation absorption by comparing NOAELs in toxicity studies.

As outlined in PRD2012-05, an additional factor of 3-fold was applied for extrapolation from a LOAEL to a NOAEL. This approach is consistent with PMRA's Science Policy Note SPN2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*.

Comment on 3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

The registrant proposes that the requirement for use of closed mixing/loading equipment by commercial seed treatment facilities be removed based on previously assessed surrogate studies, on corn seed and small grain cereal seed, which show that the mix/load method used was an open system (Regulatory Note REG2004-06, *Clothianidin, Poncho 600 and Seed Treatment Insecticide*), as opposed to a closed system as the PMRA concluded, and that the dermal absorption value used for ipconazole (100%) was overly conservative. The registrant proposes that a conservative absorption value of 10% would be appropriate as based on the low water solubility of ipconazole and the use of a 5% dermal absorption value by the UK-CRD and use of a 3% dermal absorption value by the USEPA.

PMRA Response on Corn Seed Surrogate Study

The corn seed passive dosimetry study is used as a surrogate study for estimating commercial worker exposure during seed treatment. The purpose of this study was to quantify inhalation and dermal exposure of workers during commercial seed treatment of canola seed with Oftanol Technical Insecticide (containing the active ingredient isofenphos) and Benlate-T at an application rate of 12 g isofenphos/kg seed. Monitoring was done for isofenphos only. In the study, the mixer prepared the seed-coating material by combining 90 L of an adhesive substance, 36 kg of powdered Benlate-T fungicide, and 4.5 kg of dye in a 300 L mixing tank.

Thirty-six liters of Oftanol Technical Insecticide were pumped into the mixing tank from a 55 gallon drum with a hand-operated drum pump through a hose. The mixing tank cover was replaced and the mixture was agitated briefly. In the study, the mixer spent the majority of his time emptying 25 kg bags of untreated seed into a floor level hopper for elevation to the batch blending machine on the second level.

The method employed for mixing and loading of the monitored ingredient, isofenphos, is not characteristic of open mixing and loading. Open mixing and loading involves an "open pour" scenario, where a worker pours the seed treatment product one or more times into a measuring cup, another container or the open seed treater reservoir. The expected exposure from "open pouring" could include splashing of the product onto the worker, and result in significant dermal and inhalation exposure.

In the surrogate study, the mixer attached a hand pump to the large drums of Oftanol Technical and pumped the product through a hose that he placed into the top of the mixing tank. Since the product was contained, the exposure from this scenario would underestimate exposure during open mixing and loading involving open pouring. Although the study had been used in the past as an example of open mixing and loading, given the age of the study it was recently re-examined in the context of the open pour scenario noted above. Although the surrogate study is not representative of current standards for closed mixing and loading, it would underestimate worker exposure during open transfer. Therefore, it cannot be used to support registration of open mixing and loading in commercial seed treatment facilities.

PMRA Response on the Small Grain Cereal Seed Surrogate Study

The small grain seed passive dosimetry study is used as a surrogate study for estimating commercial worker exposure during seed treatment. The purpose of this study was to quantify inhalation and dermal exposure of workers during commercial wheat seed treatment with Baytan 312 FS (containing the active ingredient triadimenol).

At all 3 facilities, a worker (mixer/calibrator) was monitored during preparation and mixing of the seed treatment solution, calibration, and disassembly of the treatment equipment. At each facility, this worker prepared the treatment mixture by weighing each component by hand, and placing them into a 200 L drum. The mixture consisted of approximately 6 kg seed colourant, 43 kg Baytan 312 FS, and 156 kg water. The drum served as a temporary mix tank which the worker rolled back and forth to mix the components. The drum was then attached to the treatment equipment using hoses. This worker also calibrated the treatment equipment at the onset of the study at each facility. After completion of the Baytan 312 FS treatment, the worker was monitored during disassembly of the treatment equipment. This included disconnecting the hoses and fittings from the drum containing the treatment mixture, cleaning the drum and loading it into the transport van.

The highest dermal and inhalation exposure was found for mixers/calibrators, who were in fact performing 'open pour' mixing. However, the study authors stated that the other activities and equipment associated with the mixers/calibrators were not typical for most treatment plants, and this scenario was not considered relevant for exposure assessment. Based on this rationale and current standards of practice, the exposure values (for treaters) were selected as the surrogate study values for the current risk assessment by PMRA for ipconazole, despite the previous use of mixer/calibrator exposure values from this study for open pour scenarios. Since relevant exposure to mixers/loaders cannot be addressed by this study, a closed system would have to be used so as not to underestimate exposure to mixer/loaders. Therefore, this surrogate study cannot be used to support open mixing and loading in commercial seed treatment facilities.

PMRA Response on Dermal Absorption

Although there may be opportunities to refine the conservative dermal absorption value for ipconazole, a refined dermal absorption value will not impact the outcome of the seed treatment risk assessment. The personal protective equipment and type of mixing and loading equipment required are based on the level of protection outlined in the surrogate studies used to evaluate exposure. It is not possible to extrapolate to less protective scenarios; therefore, the personal protective equipment and mixing and loading equipment must be equivalent to, or more protective than, what was used in the surrogate exposure studies.

Comment on 4.1 Fate and Behaviour in the Environment

The registrant suggested changes to the Proposed Registration Decision PRD2012-05, *Ipconazole* for various text and data related to hydrolysis, aerobic biotransformation, mobility, and phototransformation in water of ipconazole.

PMRA Response

As part of the original submission, the registrant provided studies, data, and endpoints for these areas of chemistry and fate. The PMRA, as part of the review and in keeping with PMRA risk assessment tools and methods, reanalyzed these submitted data. This resulted in different values from those provided by the applicant. The information presented in the Table 13 of PRD2012-05 represents results of the PMRA review only. The suggested changes by the registrant represent the information from their original results, which differed from those of the PMRA. The PMRA utilized the results generated by the reanalysis of company data. The specific areas of suggested changes to Table 13 of the PRD2012-05 are addressed below.

Terrestrial Hydrolysis

No study or data were submitted by the company for terrestrial hydrolysis. The PMRA does not require such a study; therefore, the "N/A" under each heading in the table remains applicable.

Biotransformation in aerobic soil

The PMRA utilizes a program based on non-linear least squares to calculate biotransformation. The program provides output for three models, SFO (simple first order), DFOP (double first order parallel), and FOMC (first order multi-compartment), and associated error. For each output, the 'best fit' model is used, which often accounts for differences with values calculated by the registrant if their model is not the same.

Adsorption in soil

To calculate the adsorption coefficient for a given soil, the PMRA uses the slope of the regression between soil and supernatant concentration. The method used by the registrant was unclear. The values presented in Table 13 of the PRD2012-05 represent the results of the PMRA analysis.

Phototransformation in water

The suggested value given by the registrant of a half life equal to 32 days is correct; the value given in Table 13 of 34 days is a typographical error. However, the comment of "Stable" should remain, as this is terminology used by the PMRA under such circumstances.

Summary

Based on the information provided, the PMRA does not agree with the registrants suggested revisions, other than the correction of the half life noted under phototransformation in water.

References

PMRA Document Number Reference

1368584 2006, Ipconazole Toxicity Study by Dietary Administration to Han Wistar Rats for 13 Weeks (amended final report), DACO: 4.3.1

1368595 2006, Ipconazole: A 28-Day Dermal Toxicity Study in Rats, DACO: 4.3.5

1368600 2006, Ipconazole: A 4-Week Inhalation Toxicity Study, DACO: 4.3.6

1368601 2006, Ipconazole: A 4-Week Inhalation Toxicity Study in the Rat via nose-only exposure, DACO: 4.3.6